SYNTHESIS AND PHARMACOLOGICAL STUDIES OF IMIDAZOLONE, BENZOTHIAZOLE, QUINOXALINE, OXADIAZOLE, TRIAZOLE AND QUINAZOLINONE ANALOGUES RELATED HETEROCYCLES

Heterocyclic Chemistry has great importance to the Medicinal Chemists. Large numbers of various heterocyclic compounds are being used as therapeutic agents and these compounds are also essential for the human life. Looking to the development and the demand, to study the pharmacological profile of new heterocyclic compounds will be carried out. A large number of drugs and biologically relevant molecules contain heterocyclic systems. Often the presence of hetero atoms or groupings imparts preferential specificities in their biological responses. Amongst the heterocyclic systems, compounds containing hetero atoms such as nitrogen and/or sulfur e.g., imidazolone, benzothiazole, quinoxaline, oxadiazole, triazole, quinazolinone etc. have great importance due to their diverse biological activity. Hence, we have also decided to work which is dealing with the synthesis and biological studies of such nitrogen and sulfur containing heterocycles.

The imidazolinones **(1-6)** have been associated with a wide range of therapeutic activities **(7, 8)** such as anticonvulsant, sedative and hypnotic, potent CNS depressant, antihistamine, anti filarial, bactericidal, fungicidal, anti-inflammatory, antiparkinsonian, antihypertensive and anthelmintic. Recently new imidazoline derivatives were reported for their anti-inflammatory, herbicidal and hypertensive activities **(9, 10)**.

Benzothiazoles were synthesized from anilines. Benzothiazoles demonstrated significant anti-tubercular activity **(11)**. Benzothiazoles and its derivatives possessed some significant activity e.g. anti-inflammatory **(12)**, anti-HIV **(13)**, antimalarial **(14)**, antitumor **(15)**, anti-viral **(16)**, anticonvulsant **(17)** and antidiabetic **(18)**.

Quinoxaline derivatives have been reported to possess a wide variety of biological activities like antihistaminic **(19)**, antimycobacterial **(20)** and antimicrobial **(21)** activity. Triazoles demonstrated significant antitubercular activity **(22)**.

1,3,4-Oxadiazoles possess significant pharmacological importance, its derivatives demonstrated wide range of biological activities such as anti-HIV **(23)**,

antitubercular **(24)**, antiviral **(25)**, antimalarial **(26)**, antimicrobial **(27)**, anticancer **(28)**, anticonvulsant **(29)**, anti-parkinsonian **(30)** and analgesic **(31)**.

1,2,4-Triazoles demonstrated significant antitubercular activity **(32)**. Triazoles demonstrated anti-tubercular activity as N-acetyltransferase inhibitor, which decrease the mycobacterial cell wall lipids **(33)**, triazoles possessed significant activity e.g. anticancer **(34)**, anti-inflammatory **(35)**, anti-HIV **(36)**, antimalarial **(37)**, antitumor **(38)**, anti-viral **(39)** and anticonvulsant **(40)**.

The quinazolin-4-(3*H*)-one ring system is considered as an interesting moiety due to its wide range of biological properties, which include antitubercular **(41)**, antibacterial **(42)**, antifungal **(43)**, anticancer **(44,45),** anti-HIV **(46)**, anthelmintic **(47)**, anti-inflammatory **(48-51)**, antihypertensive **(52)**, antidiabetic **(53)**, CNS depressant **(54, 55)** activities, etc.

Looking to the literature survey and our previous work on benzothiazole **(56)**, oxadiazole, triazole **(57)** and quinazolinone molecular framework by incorporating different substituted amines, acetamides, thiazolidinone, 4-oxazolidinones and 2-azetidinones on C-3 position of quinazolinone and studied their antimicrobial activities therefore, we initiated the work to synthesize several new heterocycles such as oxazolone from hippuric acid, imidazolone from oxazolone, benzothiazole from substituted amines, hydrazide of quinoxaline, triazole from oxadiazole, oxadiazole from hydrazide and substituted various acids, quinazolinone from benzoxazin via various substituted acid and anthranilic acid.

Present thesis consists of **Eight Chapters.**

Chapter I contains scope of present work and further divided in to **four Sections** of introduction and literature review;

Section I : This section contains introduction and literature review of Quinazolinone

Section II : This section contains introduction and literature review of 1,2,4-Triazole

Section III : This section contains introduction and literature review of Quinoxaline

Section IV : This section contains introduction and literature review of imidazolone

Chapter II contains four sections including experimental, spectral and biological (antibacterial, antifungal and antitubercular) studies.

Section I : Synthesis of 7-Chloro-2-(heterocycles)-3-(4-(6-methylbenzo[*d*] thiazol-2-yl)phenyl)quinazolin-4(3*H*)-one

Section II : Spectral studies

Section III : Biological studies (antibacterial, antifungal and antitubercular)

Section IV : This section contains result and discussion and overall conclusion of synthesized compounds in this series.

Chapter III contains four sections including experimental, spectral and biological (antibacterial, antifungal and antitubercular) studies.

Section I : Synthesis of N-(3-(heterocycles)-5-((1-phenyl-1*H*-1,2,4-triazol-3-yloxy)methyl)-4*H*-1,2,4-triazol-4-yl)-2-(quinoxalin-2-yloxy)acetamide

Section II : Spectral studies

Section III : Biological studies (antibacterial, antifungal and antitubercular)

Section IV : This section contains result and discussion and overall conclusion of synthesized compounds in this series.

Chapter IV contains four sections including experimental, spectral and biological (antibacterial, antifungal and antitubercular) studies.

Section I : Synthesis of N-(3-(heterocycles)-5-((quinoxalin-2-yloxy)methyl)-4*H*-1,2,4-triazol-4-yl)-2-(1-phenyl-1*H*-1,2,4-triazol-3-yloxy)acetamide

Section II : Spectral studies

Section III : Biological studies (antibacterial, antifungal and antitubercular)

Section IV : This section contains result and discussion and overall conclusion of synthesized compounds in this series.

Chapter V contains four sections including experimental, spectral and biological (antibacterial, antifungal and antitubercular) studies.

Section I : Synthesis of 2-(3-(heterocycles)-5-((quinoxalin-2-yloxy)methyl)-4*H*-1,2,4-triazol-4-ylamino)-2-oxoethyl 2,3,4,5-tetrafluorobenzoate

Section II : Spectral studies

Section III : Biological studies (antibacterial, antifungal and antitubercular)

Section IV : This section contains result and discussion and overall conclusion of synthesized compounds in this series.

Chapter VI contains four sections including experimental, spectral and biological (antibacterial, antifungal and antitubercular) studies.

Section I : Synthesis of 2-(3-(heterocycles)-5-((quinoxalin-2-yloxy)methyl)-4*H*-1,2,4-triazol-4-ylamino)-2-oxoethyl 2,3,4,5,6-pentafluoro benzoate

Section II : Spectral studies

Section III : Biological studies (antibacterial, antifungal and antitubercular)

Section VI : This section contains result and discussion and overall conclusion of synthesized compounds in this series.

Chapter VII contains four sections including experimental, spectral and biological (antibacterial, antifungal and antitubercular) studies.

Section I : Synthesis of *N*-(3-(heterocycles)-5-((quinoxalin-2-yloxy)methyl)-4*H*-1,2,4-triazol-4-yl)-1*H*-benzo[*d*]imidazol-2-amine

Section II : Spectral studies

Section III : Biological studies (antibacterial, antifungal and antitubercular)

Section IV : This section contains result and discussion and overall conclusion of synthesized compounds in this series.

Chapter VIII contains four sections including experimental, spectral and biological (antibacterial, antifungal, antitubercular, anti-HIV-1 and anticancer) studies.

Section I : Synthesis of (Z)-1-(4-(6-methylbenzo[*d*]thiazol-2-yl)phenyl)-4-(substitutedbenzylidene)-2-phenyl-1*H*-imidazol-5(4*H*)-one

Section II : Spectral studies

Section III : Biological studies (antibacterial, antifungal, antitubercular, anti-HIV-1 and anticancer)

Section IV : This section contains result and discussion and overall conclusion of synthesized compounds in this series.

Analysis

All the new synthesized compounds have been proved by elemental analysis and spectral studies such as IR, ^{1}H NMR, ^{13}C NMR and Mass spectra. Antibacterial activities (MIC) against Gram-positive (*S. aureus and S. pyogenes*) and Gram-negative (*P. aeruginosa and E. coli*) bacteria by broth dilution method were compared with standard drugs gentamycin, ampicillin, chloramphenicol, ciprofloxacin and norfloxacin. Antifungal activities (MIC) against *C. albicans, A. niger and A. clavatus* by broth dilution method were compared with standard drugs nystatin and greseofulvin **(58)**. Antitubercular activity (MIC) against *M. tuberculosis* $H_{37}RV$ mycobacterium by L.J agar (MIC) method was compared with standard drug rifampicin **(59-61)**. National Cancer Institute (NCI) of United States selected two compounds to be evaluated for their *in vitro* anticancer activity. The data of screening on 60 human tumor cell lines is reported as mean graph of the percent growth of the treated cells using procedure reported by NCI. Compounds were tested against the human immunodeficiency virus type-1 (HIV-1), in MT-4 cell-based assays by assessing the reduction of the HIV-1 induced cytopathogenicity, using efavirenz as reference inhibitor and the results are expressed as EC_{50} values. The cytotoxicity was evaluated in parallel with the antiviral activity, in mock-infected MT-4 cells and the results are expressed as CC_{50} values **(62, 63)**.

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